

# Future modalities to assess fracture healing

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## Abstract

**Objectives:** Fracture healing remains a complex process routinely evaluated in clinical practice with sequential radiographs. Assessing the presence of union is a critical issue in patient care, with widespread implications in terms of overall decision-making and postoperative rehabilitation. Nonunion assessment, whether it be with radiographs or more advanced imaging, has far-reaching consequences for the patient in addition to the health care system. The purpose of this review was to explore new, emerging modalities for the assessment of fracture healing.

**Methods:** A review of the current, relevant literature regarding the use of serologic markers and radiostereometric analysis was conducted, and the results were summarized.

**Results:** Emerging techniques to assess fracture healing have been evaluated, including the use of serologic markers as well as radiostereometric analysis. Their potential applications extend beyond the simple assessment of a united fracture, with the capacity to predict nonunion at earlier phases of care.

**Conclusions:** While early results appear promising, the current application of serologic markers and radiostereometric analysis as a means to assess fracture healing remains limited, and future larger-scale studies are needed to establish concrete and tailored guidelines for use.

**Keywords:** fracture healing, radiostereometric analysis, serologic markers

## 1. Introduction

Routine radiographic imaging has remained the mainstay in orthopaedic practice to assess clinical progression of healing in fractures. Determining fracture union is critical for patient care, with far-reaching clinical implications in the overall decision-making process for functional advancement. The development of nonunions has far-reaching consequences not only for the patient, but also for the medical system. Indeed, the treatment of nonunions requires a significant utilization of resources and has a tremendous impact on patient outcomes.<sup>[1-4]</sup> However, healing is a complex, multifactorial process, and radiography remains a somewhat limited, though widely used, tool to evaluate stages of healing and ultimate union.<sup>[5]</sup> This review provides an overview

of future directions that have shown promise in evaluating healing with novel modalities.

## 2. Serologic markers

Early predictors of impaired fracture healing prior to radiographic evidence would allow for earlier intervention and subsequently lower medical costs while improving patient outcomes. Serologic markers have been proposed as one method of early fracture healing detection.<sup>[6-8]</sup> Numerous biologic markers have been identified and linked with delayed fracture healing. Osteocalcin (OC) was one of the initial biomarkers studied with respect to their association with healing. In the study by Oni et al,<sup>[9]</sup> normally uniting fractures in general demonstrated higher values of OC in comparison with those with delayed healing. Similarly, the study by Ali et al<sup>[10]</sup> observed higher OC expression in normal healing as compared with impaired healing from days 4 to 28 postfracture.

Transforming growth factor B1 (TGF-B1) has also been examined as a potential marker for delayed fracture healing. TGF-B1 has been shown to be an essential regulatory molecule in fracture healing, and has been detected in the callus of human and animal fracture models.<sup>[6]</sup> In the study by Zimmerman et al,<sup>[11]</sup> TGF-B1 levels increased in both the union and delayed union group 2 weeks after trauma, but were significantly lower in the delayed union group between 2 and 4 weeks after trauma. In a prospective study involving 15 patients with normal long bone healing compared with 15 patients with delayed healing, both normal and delayed healing groups serum level of TGF-B1 increased within the first 2 weeks after fracture, but the delayed healing group demonstrated a quicker decline in serum concentrations between 2 and 4 weeks posttrauma. Furthermore, the delayed healing group was found to have a significantly lower level of serum TGF-B1 at 4 weeks compared with the healing group.<sup>[12]</sup> However, in the study by Sarahrudi et al<sup>[13]</sup> involving 9

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patients with long bone nonunions matched to 9 patients with normal healing, those patients who developed a nonunion had higher TGF- $\beta$ 1 concentrations at 6 weeks, and no significant differences in TGF- $\beta$ 1 concentrations were found in delayed and normal fracture healing groups. Although elevated levels of TGF- $\beta$ 1 in hematoma and in serum after bone fractures indicate its involvement in healing, the use of this serologic marker as a tool to assess fracture healing remains limited, and further studies with higher numbers of patients are needed to clarify its role.

Several additional molecules have been explored in humans to date. Fibroblast growth factor-2 (FGF-2) is a positive regulator of bone formation. It is synthesized by osteoblasts and induces osteoblast proliferation and differentiation, favors bone nodule formation, inhibits apoptosis of mature osteocytes, and regulates osteoclastogenesis.<sup>[14]</sup> Its importance has further been supported in studies where FGF2 knockout mice have shown decreased bone mass and formation, and have demonstrated several characteristics of age-related osteoporosis.<sup>[15,16]</sup> In the study by Granchi et al,<sup>[17]</sup> FGF-2 serum values were evaluated in 88 children and found to be significantly lower in children who did not heal after surgery.

The activity of osteoclasts can directly be determined by levels of tartrate-resistant acid phosphatase 5b (TRACP 5b) and C-terminal cross-linking telopeptide of type I collagen (CTX). TRACP 5b has been utilized in biomonitoring, and has been found to play a role in the effective control of antiresorptive processes. Furthermore, it has been used to diagnose osteoporosis, renal osteodystrophia, and malignant bone metastases.<sup>[17,18]</sup> CTX levels reflect collagen degradation, and have been shown to predict fracture risk in osteoporosis.<sup>[19]</sup> In the study by Moghaddam et al,<sup>[18]</sup> serum TRACP 5b and CTX were evaluated in 15 patients with atrophic nonunion matched to 15 patients with uneventful healing and found to be decreased at weeks 1, 4 and 8. In contrast, however, in the study by Emami et al,<sup>[20]</sup> no differences in the levels of CTX were found between patients with delayed and normal fracture healing.

Numerous interesting features related to osteoblast function, collagen production, and matrix ossification have been explored in recent work on fracture nonunion, Collagen types I and III and their role in osteoblast activity has been investigated, with serum levels of collagen I carboxy-terminal propeptide being found to reflect current type I collagen synthesis and osteoblast activity.<sup>[21-23]</sup> Collagen III amino-terminal propeptide, a cleavage product of collagen synthesis that has been reported to normalize prior to radiographic and clinical evidence of healing, has been found to be elevated at 10 weeks in tibial shaft fractures that failed to heal.<sup>[24,25]</sup> Alkaline phosphatase, an osteoblast-derived serum marker, was evaluated by Ajai et al and found to be elevated at 6 months postfracture in patients who developed nonunion or delayed union in comparison with more moderate levels observed in healed patients.<sup>[26]</sup>

The application of biomarkers to aid in early assessment of fracture healing remains a promising and potentially powerful prospect. Though numerous biomarkers have been evaluated in humans with significant findings, their use as diagnostic tools to evaluate healing remains problematic. In the systematic review by Pountos et al,<sup>[27]</sup> no robust recommendations could be made with respect to which biomarker should be used and how it should be used in the clinical setting. Serum biomarkers remain a potential, but currently limited, tool in the evaluation of clinical fracture healing.

### 3. Radiostereometric analysis

Radiostereometric analysis (RSA) was first introduced by Selvik over 20 years ago as a method utilizing sequential radiographs to perform accurate three-dimensional measurements *in vivo*.<sup>[28]</sup> RSA involves the implantation of metallic landmarks (tantalum beads) into bone or implants. The beads serve as the rigid body, with the relative position of these beads in a given body not expected to vary with time. Dual simultaneous radiographs of the patient are then used to determine the gravitation center of the rigid body, with the relative movement between gravitational centers of multiple rigid bodies providing the RSA measurement. This RSA method allows for highly accurate measurements of both translation and rotation in 3 dimensions.<sup>[29-31]</sup> Indeed, RSA has become the gold standard in the field of arthroplasty for the three-dimensional measurement of *in vivo* position changes and wear of prosthetics.<sup>[32,33]</sup>

The application of RSA in orthopaedic fracture care has been extensively studied as a method to accurately assess fracture stability over time and fracture stiffness. There have been 3 clinical studies using RSA to evaluate fracture motion in distal radius fractures.<sup>[34-36]</sup> In the study by Downing et al,<sup>[34]</sup> 9 patients treated with open reduction and volar locked plating of a distal radius fracture in addition to insertion of tantalum beads into bone fragments were evaluated. RSA examinations at day 1 and at weeks 2, 6, 26, and 52 weeks were performed. They concluded that the precision of this RSA method was sufficient to observe inducible movements that occurred during fracture healing.<sup>[34]</sup> In the randomized study by Kopylov et al,<sup>[35]</sup> RSA was used to compare healing in 23 patients treated with either use of a dorsal splint and Norian SRS with immobilization for 2 weeks or with external fixation for 5 weeks. At the time of the operation, the fracture fragments were marked with tantalum markers in order for loss of reduction to be assessed both during the immobilization and after mobilization. They determined that 5 weeks of immobilization was sufficient for healing with external fixation as displacement of the fragments along the longitudinal axis was less than 2 mm.<sup>[35]</sup> In the study by Madanat et al,<sup>[36]</sup> 15 patients with OTA type C fractures of the distal radius treated with volar locked plating were evaluated. Interestingly, they reported that significant translational and rotational migration were present during the first 2 weeks after fixation, but that inducible fracture micromotion was present up to 18 weeks, even after radiographic union. They concluded that while RSA seems to have potential as a novel tool, the method remains technically challenging.<sup>[36]</sup>

Femoral neck fractures have also been examined using RSA to not only assess union, but also femoral head viability. In the study by Ragnarrson et al, it was observed that lack of micromotion at 6 months implied healing, while fracture stabilization between 9 and 12 months was associated with avascular necrosis or delayed union in 4 of 6 patients. For those patients who had continued micromotion after 12 months, healing did not occur.<sup>[37]</sup> Differentially loaded RSA, which allows for the measurement of inducible micromotion under physiologic loading, was used to evaluate 16 patients treated for femoral neck fractures. Fracture unions were characterized by the absence of permanent fracture-site displacement by 12 weeks. However, the authors noted particular difficulty in implanting the tantalum markers in the femoral head.<sup>[38]</sup>

Recently, the utility of RSA to predict nonunion was evaluated in patients treated for distal femur fractures. In the study by Galea et al,<sup>[39]</sup> 16 patients treated for distal femur fractures with a lateral locked plate were evaluated with RSA. The authors

reported that on the basis of RSA, healing in the majority of distal femur fractures treated with plate fixation occurred between 6 weeks and 3 months. Interestingly, the application of RSA would have flagged the 2 patients who required revision surgery for nonunion much earlier in their treatment as those patients had persistent inducible micromotion at 3 months.<sup>[39]</sup> This could serve as a particularly useful tool to surgeons, as distal femur fractures represent particularly troublesome fractures, with 75% of reported implant failures occurring after 3 months, and 50% occurring after 6 months.<sup>[40]</sup>

The use of RSA has also been reported when evaluating tibial plateau and ankle fractures. Larsson et al<sup>[41]</sup> used RSA to study the use of calcium phosphate cement augmentation as a subchondral bone void filler in comparison with conventional iliac crest bone graft, and found that calcium phosphate provided greater stability of the elevated articular fragment, even with earlier weight bearing. With respect to ankle fractures, Ahl et al observed that early weight bearing did not compromise the stability of malleolar fractures treated with internal fixation based on RSA.<sup>[42,43]</sup> While the use of RSA in these studies was not specifically for the purpose of assessing fracture healing, they demonstrate the potential for widespread application of RSA to different aspects of research and fracture care.

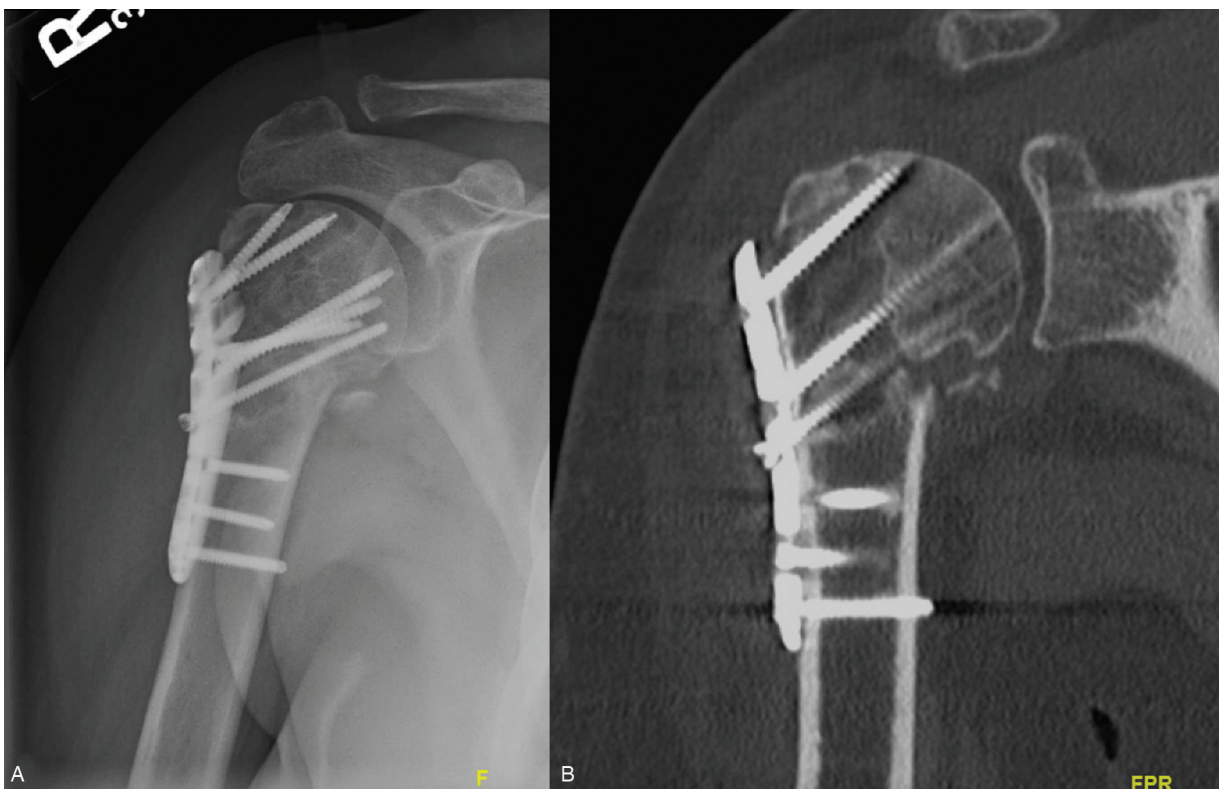
Radiostereometric analysis has been utilized in numerous clinical trials for over 30 years. It has been shown to be an accurate, precise, and safe method in evaluating various aspects of fracture care, from healing to the possibility of early detection of nonunion. While its applicability remains wide, there remain challenges with its execution, including difficulty with implantation in certain areas. Furthermore, assessment of inducible

micromotion at various stages of fracture healing remains limited, with only small patient cohorts examined to date. However, RSA does represent a potentially powerful tool in fracture care, and one that continues to be explored.

#### 4. Conclusions

Fracture union is traditionally evaluated based upon sequential radiographs to monitor the presence of bridging callus and the dissolution of fracture lines.<sup>[44]</sup> Despite the widespread use of this modality, the criteria used to judge union can vary between surgeons, and can at times be obscured by implants (Fig. 1).<sup>[45,46]</sup> Furthermore, there has been little consensus as to the timing of radiographic union, with criteria for union that can be challenging to apply to patients treated with plate application. The use of advanced imaging modalities, specifically computed tomography (CT), has become increasingly popular to assess for union. However, there is evidence to suggest that the use of CT may “over diagnose” the presence of a nonunion, with particularly poor specificity for long bone fractures.<sup>[47]</sup> In addition, the use of CT at multiple time points is cumbersome, expensive, and exposes the patient to high-radiation doses.

Other modalities have been proposed and evaluated as potential tools to aid in the assessment of fracture healing. The use of serologic markers has been proposed as 1 method of early fracture-healing detection. Numerous serologic markers have been evaluated, including osteocalcin, TGF-B1, FGF-2, TRACPB 5b, CTX, and Collagen III amino-terminal propeptide. However, at present, there remains a lack of consensus with regard to the optimal biomarker and how it should be utilized,



**Figure 1.** A, Anteroposterior shoulder radiograph of a proximal humerus in a 27-year-old-female at 8 months postsurgery. B, Computed tomography scan showing a clear nonunion at the surgical neck.

and the general conclusion is that serologic markers are a potential, but currently limited, tool in the assessment of fracture healing.

The use of RSA has also been proposed as an alternative modality to assess fracture healing. First introduced over 20 years ago, the utility of RSA has rapidly expanded, and has become the gold standard to evaluate the three-dimensional measurement of in vivo position changes and wear of prosthetics in total joint arthroplasty.<sup>[32,33]</sup> With respect to fracture healing, RSA has been extensively studied to assess fracture motion and stability. However, there remain challenges with implantation, and evaluation of inducible micromotion throughout the various stages of healing is limited. While the application of these modalities appears to be promising, they currently remain limited tools in the evaluation of clinical fracture healing, and future clinical studies with larger numbers are needed.

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